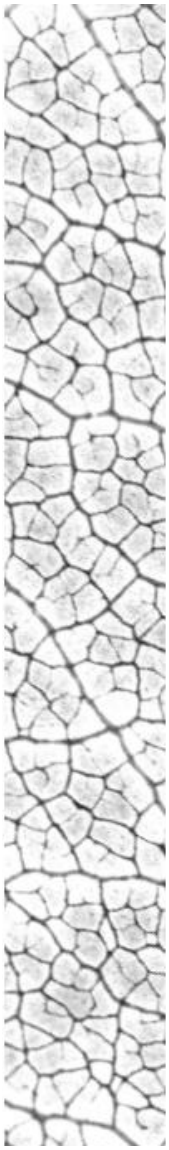

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Advantages and disadvantages of experimental glaucoma models

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Abstract
Glaucoma is a disease accompanied by a progressive degenerative lesion of the retinal ganglion cells and the optic nerve, being one of the leading causes of blindness all over the world. The search for the new drugs for the treatment of glaucoma, aimed directly at reducing intraocular pressure and neuroprotection, and in some cases neuroregeneration, is impossible without the creation of appropriate experimental models. The current variety of models does not always provide a sufficient level of functional changes or is accompanied by a number of disadvantages that impede further research. There is a wide variety of glaucoma models. This article discusses the main ones, as well as describes the advantages and disadvantages of glaucoma models performed in small laboratory animals. Hypertensive and normotensive models of glaucoma are described, which correlates with human pathogenesis. This review forms a representation and describes most models of glaucoma in rodents. The search for models of certain forms of glaucoma remains as an indisputable fact. Based on testable hypothesis and experimental validity this data should be interpreted in the context of the experiment. Despite modern achievements, the improvement of experimental techniques and the search for new models continues till the present day.

Keywords: glaucoma, neurodegeneration, renoprotective, ganglionic cells, pathology model

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INTRODUCTION

Glaucoma, a disease accompanied by a progressive degenerative lesion of the retinal ganglion cells (RGCs) and the optic nerve, represents one of the leading causes of blindness worldwide. Considering the complexity of the glaucoma formation there are many pathology development models (Biswas, Wan, 2018). Rodent models remain preferable among the available animal models.It is associated with the possibility of genetic formation of pathology and experimental modeling. In addition, the choice of rodents is due to the similarity of the anatomical structure of human and rodent eyes (Daimon, et al. 1997). their simplicity and economic feasibility (McKinnon, Schlamp, Nickells, 2009).

A constant search for new highly effective pharmacologically active substances aimed at glaucoma treatment is not possible without appropriate models characterized by similar pathogenetic pathways for the pathology development. That ensures the relevance of this experimental pharmacology direction and was used as the basis for writing the article.

The main risk factor for most forms of glaucoma is increased intraocular pressure (IOP) (De Moraes, Liebmann, Levin, 2017). Therefore all models can be divided into hypertensive and normotensive or hypotensive models.

MAIN PART

Hypertensive Glaucoma Models

Most experimental models that induce an increase in IOP are based on eliminating the outflow of aqueous humor. In rats and primates, outflow occurs through the trabecular meshwork, into the Schlemm's canal and through the uveoscleraloutflowpathway which defines the existing models. The most significant and often used models are the following:

Microparticle Introduction

The introduction of microparticles into the anterior chamber of the eye leads to a steady increase in IOP which ensures obstruction of the trabecular meshwork

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and reduces the outflow of intraocular fluid (Calkins, et al. 2018).This model type has great relevance for studying of acute increase in IOP and isn't used as a model for studying the chronic glaucoma form (Morgan, Tribble, 2015).

Despite the convenience of the model and the low incidence of complications, its problem is the need to re-introduce particles to maintain the necessary level of IOP and the development of RGCsdegeneration, (Yang, et al. 2012).Moreover the repeated introduction leads to the development of complications and to corneal edema which pose riskthe accuracy of IOP measurement (Biswas, Wan, 2018).

Hyaluronic Acid Introduction

This model has a similar mechanism of action to the model described earlier. Hyaluronic acid (HA) is introducedthrough the anterior chamber of the corneal-scleral limb avoiding contact with the iris and lens. Repeated injections lead to a gradual increase in the depth of the anterior chamber of the eye and increase IOP (Mayordomo-Febrer, et al. 2015.)

The disadvantage of the model is the need for repeated injections and the high risk of possible complications of the cornea and lens (Agarwal, Agarwal, 2017).

Hydrodynamic model

This model allows to increase IOP sharply.It is carried out by introducing a 30gauge needle into the anterior chamber of the eye which is connected by tubes to a reservoir filled with physiological saline (0.9% NaCl). In this case, the IOP level is controlled by the height of the reservoir (Fortune, et al. 2011).

There is known the modification of the hydrostatic model based on mechanical action on the anterior chamber of the eye (Shabelnikova, et al. 2016).and alsothe combined use of IOP increase on the background of L-NAME modeling which is typical for hypertensive neuroretinopathy (Peresypkina, et al. 2018).

In the proposed models a significant effect on the retinal vessels is observed which most probably leads to damage to the ganglion cells (Shabelnikova, et al., 2014., Levkova, et al. 2019).

Laser photocoagulation

Laser exposure is possible on the trabecular meshwork (Kwong, et al. 2013). limb zone (Yun, et al. 2014). and episcleral veins (Levkovitch-Verbin, et al. 2002.) which allows the formation of increased IOP.

The level of IOP increase after one procedure is relatively high compared with other types of glaucoma models (Ishikawa, et al. 2015.) After laser exposure to the limb (in mice) the IOP increased to 20 mmHg during the observation period of 24 weeks. (Yun, et al. 2014)

Although laser photocoagulation has many advantages, the main limitationof this model is corneal perforation, that can increase the riskof infection and affect IOP measurements using contact tonometers (Dey, et al. 2018).Also there are mentioned in the literaturecases of eye inflammation, flattening of the anterior chamber, variability in the magnitude and duration of IOP, irreversible mydriasis (Biswas, Wan, 2018).

Cauterization / ligation / intraepiscleral injection of the episleral veins

Impact on the episcleral veins is possible not only by laser photocoagulation. There are also models aimed at their cauterization (Ruiz-Ederra, Verkman, 2006). and ligation (Zhu, Zhang, Schmidt, Gidday, 2012).

YuSand co-authors demonstrated a chronic increase in IOP in female Wistar rats after ligation of 3 episcleral veins with a 10/0 nylon suture after dissection of the overlying conjunctiva and Tenon's capsule. This method provided a steady increase in IOP (24.5 ± 2.3 mmHg in the operated eyes compared to 19.7 ± 1.9 mmHg in the control eyes) for 7 months in 40% of the operated eyes. A prolonged increase in IOP caused damage to the optic disc and the death of 35% RGCsin 8 months after venous ligation (Yu, Tanabe, Yoshimura, 2006).

Another well-known obstruction method is the Moore–Morrison model (Morrison, et al. 1997). where a chronic increase in IOP is induced in the rat through the episcleral vein by the introduction of hypertonic saline (2 M). Moreover, it was found that a higher concentration of saline (> 2.0 M) caused greater destruction of the trabecular meshwork along with a higher increase in IOP, which lasted for several months. However, injection of higher concentrations of the solution also caused excessive inflammation and damage to the ciliary body. Consequently, a concentration of 1.74 M has become the standard for use in most models of chronic increase in IOP in rodents (Dey, et al. 2018.

Circumlimbal suture application around the equator of the eye

The application of an 8/0 nylon suture around the equator of the eye by approximately 1.5 mm behind the limb, with 5-6 subconjunctival anchor points, increased IOP to 58 ± 3 mmHg and remained elevated by 7–10 mmHg above baseline for 15 weeks (Liu, et al. 2015).

The described models are widely used to model pathologies in rodents. It is not possible to make a direct comparison between these methods due to the formation of a different level and duration of an increase in IOP, as well as a varying degree of variability of structural and functional losses associated with an increase in IOP.

Drug-induced elevation of IOP

The use of glucocorticoids is known to increase IOP. A steroid model of glaucoma is believed to mimic primary open-angle glaucoma in humans. Topical administration of dexamethasone in Wistar rats leads to an increase in IOP after application from 14 to 36 days (Marcus., et al. 2019).

Normotensive models

Given the existence of a normotensive form, models characterized by RGCs damage without an increase in IOP have been developed. Despite the fact that the pathophysiology mechanism of existing models does not describe the processes occurring in glaucoma, an understanding of the neurodegeneration of RGCs was obtained usingthe normotensive models. Among them are the following:

Pinching or dissection of the optic nerve

Mechanical damage to the axon of a neuron triggers a process that leads to anterograde degeneration. Pinching or segmental damage to the optic nerve was used to start the process of RGCs death. In this case, the death of RGCs in this study occurred gradually. 7 days after the injury, the number of RGCs was reduced to 47% of normal, 2 weeks after the injury, 27% of RGCs remained viable (Levkovitch-Verbin, et al. 2000).A wide range of RGCs survival rates indicates significant differences in the degree of impact and duration of the development of the model (Johnson, Tomarev, 2010).

The advantages of this model consist in the relatively rapid formation of pathology and the simplicity of the procedure (Johnson, Tomarev, 2010). In this connection, the described model makes it possible to evaluate the role of axon damage in the formation of glaucomatous damage.

Intravitreal administration of excitotoxic substances

The most widely used model is the introduction of a specific agonist of NMDA receptors of N-methyl-D-aspartic acid. Intravitreal administration of high doses (20-200 nmol) NMDA is the most common method of triggering RGCs death (Lambuk, et al. 2019).This model is used as the basis for the study of neuroprotective strategies aimed at excitotoxic damage to the central nervous system.

DISCUSSION

Taking into account the basic theories of the pathogenesis of glaucoma (biochemical, vascular, mechanical), it is worth noting the emergence of new hypotheses in the theory of the development of glaucoma. This can be used as a key to solving this problem and as an impetus for the development of new animal models. In experimental pharmacology, much attention is paid to models which results can be extrapolated to humans. Compounds of erythropoietin as neuroprotectors (Shabelnikova, et al. 2015).and other compounds providing cyto- or neuroprotection can be very promising for further study (Martynova, 2017. Martynov, et al. 2016 – Peresypkin, ET AL. 2020)..Despite the rapid development of experimental pharmacology (Avdeeva, et al. 2019– Kim, et al., 2019-Skachilova, et al. 2017.), the improvement of directed synthesis methods, the search for drugs for the treatment of glaucoma remains highly relevant.

CONCLUSION

orms a representation and describes most models of glaucoma in rodents. Given the literature, experimentally induced models have an advantage over transgenic ones, due to the formation of pathology in a short period of time, but in turn require sophisticated equipment and trained personnel to model glaucoma. At the same time, the key role of genetic models is based on testing specific hypotheses, presenting information on pathophysiology and the potential discovery of new therapeutic goals. Despite modern achievements, the improvement of experimental techniques and the search for new models continues to this day.

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